REMARKS

Claims 1-25 are all the claims pending in the application. Claims 10-12, 18 and 21-25 have been cancelled. Claims 1-9 have been amended to incorporate the recitation of claim 10 and claims 13-17 have been amended to incorporate the recitation of claim 18. No new matter has been added.

Claim Objections

In paragraph 3 at page 2 of the Office Action, the Examiner objected to claim 2 because it states "cerebral infarction" twice.

Although the claim contains the phrase "cerebral infarction" twice, applicants respectfully submit that the phrase has two different uses in the claim. The first occurrence of the phrase "cerebral infarction" is to define the disorder itself and the second occurrence of the phrase is to modify the term "sequelae." In the second occurrence, the disorder is the "sequelae" or secondary effects of the primary disorder. Thus, withdrawal of the objection is requested, respectfully.

Claim Rejections - 35 U.S.C. § 101

In paragraph 4 at page 2 of the Office Action, the Examiner rejected claims 21-25 under 35 U.S.C. § 101 because "use" claims are not acceptable under U.S. practice.

The rejected use claims (21-25) have been canceled.

Claim Rejections - 35 U.S.C. § 112, second paragraph

In the third and fourth full paragraphs at page 3 of the Office Action, the Examiner rejected "use" claims 21-25 under 35 U.S.C. § 112, second paragraph, as being indefinite because they do not set forth any steps involved in the intended methods/processes.

The rejected use claims 21-25 have been canceled.

35 U.S.C. § 112, first paragraph

From the first full paragraph at page 4 of the Office Action to the paragraph bridging pages 8 and 9 of the Office Action, the Examiner rejected all claims under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Specifically, the Examiner believes: (i) that applicants have not enabled every therapeutic or preventive method claimed; (ii) that applicants have not enabled efficacy in humans; and (iii) that applicants have not enabled any kind of gene therapy.

For the following reasons, the rejection is overcome.

Claims 1 to 9 have been amended to recite that the HGF gene and/or VEGF gene, as the active ingredients, are in the form of HVJ-liposomes.

Further, claims 13-17 and 19-21 have been amended to recite that the HGF gene and/or VEGF gene are administered into the subarachnoid space in a human.

As stated in the present specification at page 6, lines 5 to 21, the claimed inventions are based on the new findings according to the present inventors that: (a) after transfection, the HGF gene or VEGF gene are expressed in the brain over a prolonged period of time; (b) the transfection of the HGF gene or VEGF gene can induce angiogenesis on the surface of an ischemic brain; (c) the transfection of the HGF gene or VEGF gene is effective in treating reduced blood flow in the brain caused by vascular obstruction; (d) such transfection is effective even when conducted before the obstruction occurs; and (e) the transfection of the HGF or VEGF gene can be more effectively attained by the administration of those genes into the subarachnoid space.

Such new findings are fully supported by the pharmacological data provided in the present specification.

More specifically, Example 2 of the present specification demonstrates that, after the transfection of the HGF gene or VEGF gene in the form of HVJ-liposomes, the expressed HGF or VEGF protein was detected in the brain over a prolonged period of time.

Therefore the specification contains support for the efficacy in humans of the invention of claims 1-9.

As the Examiner has also correctly pointed out in the Office Action at page 4, line 16 to page 5, line 2, Example 4 of the specification provides data establishing that reduced cerebral blood flow resulting from obstruction of the bilateral carotid arteries is increased, and reduction of cerebral blood flow resulting from obstruction of the bilateral carotid arteries is prevented by injection of HVJ-liposome complex containing HGF or VEGF gene into the subarachnoid space of rats. Example 5 provides data establishing suppression of delayed neuronal death in the hippocampus CA-region as a result of ischemic stimulation of the bilateral carotid arteries by injection of HVJ-liposome complex containing an HGF or a VEGF gene into the subarachnoid space of gerbils.

Further, Example 3 in the specification provides data showing that angiogenesis of the brain surface is caused by the transduction of the HGF gene.

Furthermore, the specification describes at page 1, line 14 to page 2, line 9 that reduced blood flow is correlated with the various cerebrovascular disorders, and that angiogenesis is also correlated with various vascular disorders.

Additionally, two articles, Hiroshi Nakane, et al., "Cerebral blood flow and metabolism in patients with silent brain infaction: occult misery perfusion in the cerebral cortex," J. Neurol. Neurosurg. Psychiatry, 1998, 65, 317-321 and No To Hattatsu, Moyamoya disease presenting initially with mental disturbance," (in Japanese) 1997, Nov., 29 (6), 471-5, copies of which are submitted herewith, show a correlation of blood flow with various cerebrovascular disorders.

In view of the foregoing, applicants respectfully submit that the present specification describes the claimed inventions of amended claims 13 to 17 and 19 to 21, which are directed to the various therapeutic methods wherein the HGF gene and/or VEGF gene are administered into the subarachnoid space in human, in such a way so as to enable a person skilled in the art to make and use the inventions.

Accordingly, the Examiner is requested, respectfully, to reconsider and withdraw the rejection.

Claim Rejections - 35 U.S.C. § 102

From page 10, first full paragraph to the paragraph bridging pages 10 and 11 of the Office Action, the Examiner rejected claims 1-9, 11, 12 and 21-25 under 35 U.S.C. § 102(b) as being anticipated over *Isner* (WO 97/14307). Also, from page 11, first full paragraph to the paragraph bridging pages 11 and 12 of the Office Action, the Examiner rejects method claims 13-17 under 35 U.S.C. § 102(e) as being anticipated by *Isner*, (USP 6,121,246).

Claims 1 - 9 have been amended by incorporating the recitation of claim 10, which has not been rejected under 35 U.S.C. § 102 in the Office Action.

Similarly, claims 13 - 17 have been amended by incorporating the recitation of claim 18, which also has not been rejected under 35 U.S.C. § 102 in the Office Action.

Thus, the rejections under 35 U.S.C. § 102 are overcome and should be withdrawn.

Claim Rejections - 35 U.S.C. § 103

From the second full paragraph at page 12 to the second full paragraph at page 13 of the Office Action, the Examiner rejected claim 10 under 35 U.S.C. § 103(a) as being unpatentable over *Isner* (WO 07/14307) in view of *Morishita et al.* (USP 6,248,722 B1). The Examiner's position is that *Isner* teaches a pharmaceutical composition comprising an HGF gene and/or VEGF gene and *Morishita et al.* teaches that the HGF vector is unstable but that the instability can be counteracted by administering HGF vector as part of an HVJ-liposome.

Neither *Isner* nor *Morishita et al.* teach or even suggest that the HGF gene or VEGF gene in the form of HVJ-liposome is effective for the treatment of cerebrovascular disorders.

Thus, the agents of amended claims 1 to 9 should not be made obvious over *Isner* in view of *Morishita et al.*

From the third full paragraph at page 13 of the Office Action to the paragraph bridging pages 14 and 15 of the Office Action, the Examiner rejected method claims 19 and 20 under 35 U.S.C. § 103(a) as being unpatentable over *Isner* '246 in view of *Mann et al.* (USP 6,199,554).

The Examiner's position is that *Isner* teaches a method of treating ischemic tissue by injecting the tissue with an effective amount of either or both of VEGF gene and HGF gene, and

Mann et al. teach promoting revascularization and prolonging the therapeutic effect by injecting VEGF or HGF protein along with the corresponding nucleic acid molecule. The Examiner concludes that one of ordinary skill in the art, wanting to optimize the gene therapy taught by *Isner* would readily administer the VEGF gene and/or the HGF gene with VEGF and/or HGF protein in view of *Mann et al.,* and expect to get a more prolonged therapeutic effect.

For the following reasons, the rejection is traversed.

Applicants respectfully submit that *Mann et al.* '544 does not teach that the gene can be administered with protein. Rather *Mann et al.* teach that because of the nature of the plasmid that is injected, protein production from the plasmid DNA could be sustained and, as a result, no further plasmid administration would be needed. There are no teachings of administering the protein along with the DNA. Further, *Mann et al.* do not teach that gene therapy can be optimized by administering the gene with the protein. Rather, the improved results *Mann et al.* see are attributed to combining gene therapy with laser injury.

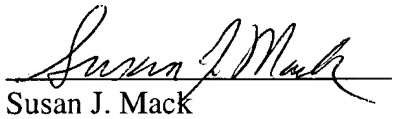
Further, claims 19 and 20 are dependent from amended claim 13, which recites that the HGF gene or VEGF gene is administered into the subarachnoid space. This administration route is neither taught nor suggested by *Isner* or *Morishita et al.*

In view of the above, applicants request the Examiner to reconsider and remove the rejections under 35 U.S.C. § 103.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: January 28, 2003

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 10-12, 18 and 21-25 are canceled.

The claims are amended as follows:

1. (Amended) A therapeutic or preventive agent for cerebrovascular disorders, said agent comprising, as an active ingredient, an HGF gene and/or a VEGF gene, wherein said HGF gene and said VEGF gene are in the form of HVJ-liposomes ~~as an active ingredient~~.

3. (Amended) A therapeutic or preventive agent for reduced blood flow in the brain comprising, as an active indredient, an HGF gene and/or a VEGF gene, wherein said HGF gene and said VEGF gene are in the form of HVJ-liposomes ~~as an active ingredient~~.

4. (Amended) A promoting agent for angiogenesis in the brain comprising, as an active ingredient, an HGF gene and/or a VEGF gene, wherein said HGF gene and said VEGF gene are in the form of HVJ-liposomes ~~as an active ingredient~~.

5. (Amended) A suppressing agent for neuronal death in the brain comprising, as an active ingredient, an HGF gene, wherein said HGF gene is in the form of an HVJ-liposome ~~as an active ingredient~~.

7. (Amended) A suppressing agent for apoptosis of nerve cells in the brain comprising, as an active ingredient, an HGF gene, wherein said HGF gene is in the form of an HVJ-liposome ~~gene as an active ingredient~~.

8. (Amended) The agent according to any one of claims 1-7 which comprises an HGF gene and/or a VEGF gene as an active ingredient and which is to be used in combination with HGF protein and/or VEGF protein.

9. (Amended) The agent according to claim 8 which comprises an HGF gene as an active ingredient and which is to be used in combination with HGF protein.

13. (Amended) A therapeutic or preventive method for cerebrovascular disorders comprising introducing an HGF gene and/or a VEGF gene into the subarachnoid space in humans.

14. (Amended) A therapeutic or preventive method for reduced blood flow comprising introducing an HGF gene and/or a VEGF gene into the subarachnoid space in humans.

15. (Amended) A method of promoting cerebral angiogenesis comprising introducing an HGF gene and/or a VEGF gene into the subarachnoid space in humans.

16. (Amended) A method of suppressing neuronal death in the brain comprising introducing an HGF gene into the subarachnoid space in humans.

17. (Amended) A method of suppressing apoptosis of nerve cells in the brain comprising introducing an HGF gene into the subarachnoid space in humans.